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U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: WFG/12544

U.S. APPLICATION NO (If known, see 37 CFR 1.5): 09/868215

INTERNATIONAL APPLICATION NO	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/DE99/03974	13 December 1999	16 December 1998

TITLE OF INVENTION: SYNTHETIC NUCLEIC ACID PARTICLE

APPLICANT(S) FOR DO/EO/US: JUNGHANS, Monika; ZIMMER, Andreas; KREUTER, Jorg

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [ ] This is an express request to promptly begin national examination procedures (35 U.S.C. 371(f)).
4. [X] The US has been elected by the expiration of 19 months from the priority date (PCT Article 31).
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is attached hereto (required only if not communicated by the International Bureau).
   b. [X] has been communicated by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [X] An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are attached hereto (required only if not communicated by the International Bureau).
   b. [ ] have been communicated by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.
8. [ ] An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 16 below concern document(s) or information included:

11. [X] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [X] Other items or information:

International Search Report.
Application Data Sheet.

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/868215	PCT/DE99/03974	WFG/12544

17. ☒ The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1000.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$860.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$710.00**

International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$690.00**

International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**

	CALCULATIONS PTO USE ONLY	
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 860.00	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$ 130.00	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	23 - 20 =	3	X **$18.00**	$ 54.00	
Independent claims	3 - 3 =	0	X **$80.00**	$ 0.00	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$270.00**	$ 0.00	
TOTAL OF ABOVE CALCULATIONS =				$ 1,044.00	
☒ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.				$ 522.00	
SUBTOTAL =				$ 522.00	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$ 0.00	
TOTAL NATIONAL FEE =				$ 522.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$ 0.00	
TOTAL FEES ENCLOSED =				$ 522.00	
				Amount to be refunded:	$
				charged:	$

a. ☒ A check in the amount of $ 522.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 18-0160 in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 18-0160. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO

Customer No. 007609
Rankin, Hill, Porter & Clark LLP
700 Huntington Building
925 Euclid Avenue
Cleveland, Ohio 44115-1405

SIGNATURE

David E. Spaw

NAME

34732

REGISTRATION NUMBER

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Monika Junghans et al.	
Serial No.:	N/A	Art Unit: N/A
Filing Date:	Herewith	
International Application No.:	PCT/DE99/03974	
International Filing Date:	13 December 1999	
Title:	SYNTHETIC NUCLEIC ACID PARTICLE	
Examiner:	N/A	
Docket No.:	WFG/12544	

PRELIMINARY AMENDMENT "A"

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Please amend the above-identified application, prior to examination thereof, in the following manner.

Express Mail Label No.: EL518109713US

IN THE CLAIMS:

Please cancel claims 1-27 without prejudice or disclaimer of the subject matter contained therein.

Please add the following new claims 28-50 as follows:

28. (New) Synthetic particle consisting of at least one nucleic acid sequence or nucleic acid derivative sequence and one protein having a molecular weight in the range from 3900 to 4300 and consisting predominantly of arginine.

29. (New) Synthetic particle according to Claim 28, where the protein is selected from the following group: protamine, protamine base, protamine derivatives or salts, preferably protamine sulfate or protamine chloride.

30. (New) Synthetic particle according to Claim 28, where the nucleic acid sequence is in single-stranded form.

31. (New) Synthetic particle according to Claim 28, where the nucleic acid sequence is an oligonucleotide or a derivative thereof.

32. (New) Synthetic particle according to Claim 31, where the oligonucleotide consists of at least 5 nucleotides.

33. (New) Synthetic particle according to Claim 31, where the derivative is a phosphorothioate or an anionic derivative.

34. (New) Synthetic particle according to Claim 28, where the average diameter of the particle is in the range from 10 nm to 100 gym.

35. (New) Synthetic particle according to Claim 28, where the particle carries a surface electric charge.

36. (New) Synthetic particle according to Claim 35, where the surface charge is in the range from -40 mV to +40 mV.

37. (New) Process for the preparation of synthetic particles according to any of the preceding claims, with the following steps:

a) preparation of an aqueous first salt-free solution containing a protein having a molecular weight in the range from 3900 to 4300, the protein consisting predominantly of arginine,

b) addition to the first solution of a second salt-free solution containing a nucleic acid sequence or nucleic acid derivative sequence and

c) mixing of the first and second solution.

38. (New) Process according to Claim 37, where the molar ratio of nucleic acid sequence or nucleic acid derivative sequence to protein is adjusted to produce a predetermined surface charge.

39. (New) Process according to Claim 37, where the protein is selected from the following group: protamine, protamine base, protamine derivatives or salts, preferably protamine sulfate or protamine chloride.

40. (New) Process according to Claim 39, where protamine, protamine base, protamine derivatives are obtained from salmon sperm.

41. (New) Process according to Claim 37, where the nucleic acid sequence is in single-stranded form.

42. (New) Process according to Claim 41, where the nucleic acid sequence is an oligonucleotide or a derivative thereof.

43. (New) Process according to Claim 42, where the oligonucleotide consists of at least 5 nucleotides.

44. (New) Process according to Claim 42, where the derivative is a phosphorothioate or an anionic derivative.

45. (New) Process according to Claim 37, where the diameter of the particle is in the range from 10 nm to 100 μm.

46. (New) Process according to Claim 37, where the particle carries a surface electric charge.

47. (New) Process according to Claim 37, where the surface charge is in the range from -40 mV to +40 mV.

48. (New) Use of a protein having a molecular weight in the range from 3900 to 4300 and consisting predominantly of arginine for the preparation of a synthetic particle consisting of the protein and at least one nucleic acid sequence or nucleic acid derivative sequence.

49. (New) Use according to Claim 48, where the protein is selected from the following group: protamine, protamine base, protamine derivatives or salts, preferably protamine sulfate or protamine chloride.

50. (New) Use according to Claim 48, where the nucleic acid is an oligonucleotide which is preferably single stranded and preferably consists of at least 5 nucleotides, or a derivative thereof which is preferably in the form of a phosphorothioate.

REMARKS

If clarification of the amendment or application is desired, or if issues are present which the Examiner believes may be quickly resolved, the Examiner is invited to initiate a telephone interview with the undersigned attorney to expedite prosecution of the present application.

If there are any additional fees resulting from this communication, please charge same to our Deposit Account No. 18-0160, our Order No. WFG/12544.

Respectfully submitted,

RANKIN, HILL, PORTER & CLARK LLP

By: _____
David E. Spaw, Reg. No. 34732

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Synthetic nucleic acid particle

The invention relates to a synthetic nucleic acid particle or particles, a process for its preparation and a use.

It is known that mononucleotides bind to clupeines (G. D'Auria, L. Paolillo, R. Sartorio and S. Wurzburger (1993): Structure and function of protamines: an ^1H nuclear magnetic resonance investigation of the interaction of clupeines with mononucleotides, Biochem. Biophys. Acta, 1162, 209-216).

Also known in the prior art is the preparation of complex compounds between double-stranded oligonucleotides, polycationic polymers and lipids. Concerning this, reference is made to the following publications:

A.V. Kabanov and V.A. Kabanov (1995): DNA Complexes with polycations for the Delivery of Genetic Material into Cells, Bioconjugate Chem., 6, 7-20;

Gao and L. Huang (1996): Potentiation of Cationic Liposome-Mediated Gene Delivery by Polycations, Biochemistry, 35, 1027, 1036;

L. Sorgi, S. Bhattacharya and L. Huang (1997): Protamine sulfate enhances lipid-mediated gene transfer, Gene Therapy, 4, 961-968;

Li and L. Huang (1997): In vivo gene transfer via intravenous administration of cationic lipid-protamine-DNA (LPD) complexes, Gene Therapy, 4, 891-900.

Complex compounds of this type can be used, for example, for transfection of plasmid DNA. Where protamine bound to transferrin is used as polycation,

such complex compounds are also referred to as transferrin-protamine-DNA complexes. Complexes of this type do not form condensed DNA structures or particles (Wagner, M. Zenke, M. Cotton, H. Beug and M.L. Birnstiel (1990): Transferrin-polycation conjugates as carriers for DNA uptake into cells, Proc. Natl. Acad. Sci. U.S.A., 87, 3410-3414).

The known complex compounds can be formed only from previously formed particles or existing complexes. For this it is necessary that a lipid is also present, besides a protein. It is a disadvantage that these complex compounds cannot form particulate structures from oligonucleotides. The DNA in the complex compound is bound only by surface adsorption. It is a disadvantage that it can undergo enzymatic degradation. Finally, the known complex compounds are unsuitable for producing pharmaceuticals with a depot effect.

It is an object of the invention to eliminate the disadvantages of the prior art. It is particularly intended to indicate a stable synthetic particle and a process [lacuna] its preparation which makes a high transfection efficiency possible. It is intended where possible for the synthetic particle also to be suitable for producing pharmaceuticals with a depot effect.

This object is achieved by the features of Claims 1, 11 and 24. Expedient developments are evident from the features of Claims 2 to 10, 12 to 23 and 25 to 27.

According to the invention, a synthetic particle is formed from at least one nucleic acid sequence or nucleic acid derivative sequence and one protein having a molecular weight of 3900 to 4300. Such a synthetic particle is, in particular, stable to enzymatic degradation. It makes a high transfection efficiency

possible and makes it possible to produce pharmaceuticals with a depot effect.

According to one developmental feature, the protein consists predominantly of arginine. It is advantageous for the arginine content to be more than 60% by weight. The protein may be selected from the following group: protamine, protamine base, protamine derivatives or salts, preferably protamine sulfate or protamine chloride. The aforementioned compounds advantageously have no antigenic properties.

The nucleic acid sequence, which is advantageously in single-stranded form, may be an oligonucleotide or a derivative thereof. The oligonucleotide preferably consists of at least 5 nucleotides. The derivative may be a phosphorothioate or an anionic derivative. The oligonucleotide may be, in particular, a DNA oligonucleotide. This makes it possible to use the synthetic particles for antisense therapy.

The average diameter of the particle can be in the range from 10 nm to 100 µm, depending on the purpose of use.

The particle advantageously carries a surface electric charge which may preferably be in the range from -40 mV to +40 mV. This makes it possible to increase the transfection efficiency further.

According to the process of the invention there is provision of a process for the preparation of the synthetic particles according to the invention, with the following steps:

a) preparation of an aqueous first solution containing a protein having a molecular weight in the range from 3900 to 4300,

b) addition to the first solution of a second solution containing a nucleic acid sequence or nucleic acid derivative sequence and

c) mixing of the first and second solution.

The process makes it possible to prepare the synthetic particles according to the invention in a simple manner.

According to one developmental feature, the first and the second solution are free of salts. It is possible to adjust the molar ratio of nucleic acid sequence or nucleic acid derivative sequence to protein to produce a predetermined surface charge. The proposed variant can be carried out particularly simply.

The protein expediently consists predominantly of arginine, and it can be selected from the following group: protamine, protamine base, protamine derivatives or salts, preferably protamine sulfate or protamine chloride. Protamine, protamine base or protamine derivatives in particular can be obtained from salmon sperm. Easy and low-cost availability is thus ensured.

The nucleic acid sequence, which is advantageously in single-stranded form, may be an oligonucleotide or a derivative thereof. The oligonucleotide preferably consists of at least 5 nucleotides. The derivative may be a phosphorothioate or an anionic derivative. The diameter of the particle may be in the range from 10 nm to 100 µm, depending on the purpose of use. It may carry a surface electric charge which is expediently in the range from -40 mV to +40 mV.

According to another achievement of the object there is provision of the use of a protein having a molecular

weight in the range from 3900 to 4300 for the preparation of a synthetic particle containing at least one nucleic acid sequence or nucleic acid derivative sequence.

The protein advantageously consisting predominantly of arginine can be selected from the following group: protamine, protamine base, protamine derivative or salts, preferably protamine sulfate or protamine chloride. The nucleic acid sequence which is advantageously in single-stranded form may be an oligonucleotide preferably consisting of at least 5 nucleotides, or a derivative thereof. The derivative may be a phosphorothioate or an anionic derivative. The oligonucleotide is expediently a DNA oligonucleotide.

The synthetic particle according to the invention is advantageously formed exclusively from the nucleic acid or the nucleic acid derivative and the protein having the molecular weight in the range from 3900 to 4300. The molecular weight of the protein in a particularly advantageous embodiment is between 4000 and 4250.

Exemplary embodiments of the invention are explained in detail below by means of the drawing and by means of examples. In the drawings,

Fig. 1a shows a scanning electron micrograph of synthetic particles with a negative surface charge,

Fig. 1b shows a scanning electron micrograph of synthetic particles with a positive surface charge,

Fig. 2 shows the dependence of the particle size on the incubation time,

Fig. 3 shows the dependence of the surface charge on the protamine/oligonucleotide ratio,

Fig. 4a shows a confocal laser scanning micrograph of a first vero cell.

Fig. 4b shows a confocal laser scanning micrograph of a second vero cell.

Fig. 5 shows the dependence of the UV absorption at 260 nm on the retention time for particles differing in protamine/oligonucleotide composition.

Examples:

1. Preparation of oligonucleotide particle with negative surface charge

500 µl of a protamine solution (50 µg/ml) in double-distilled water are spontaneously added in an Eppendorf cap at room temperature to 500 µl of a likewise salt-free oligonucleotide solution (100 µg/ml). The oligonucleotides preferably present in the solution are single-stranded DNA oligonucleotides. The solution is then vigorously mixed for 1 minute with a high-speed stirrer. Particle formation starts spontaneously and is complete after half an hour. The ratio by weight between the protamine molecule employed and the oligonucleotide is about 0.75 to 1. The ratio by weight between protamine and the oligonucleotide for particle formation is about 1:2.5.

2. Preparation of oligonucleotide particle with positive surface charge

Based on the process described in Example 1 process [sic], 500 µl of a protamine solution (250 µg/ml) in

double-distilled water are added spontaneously in an Eppendorf cap at room temperature to 500 µl of a likewise salt-free oligonucleotide solution (100 µg/ml). The molar ratio between protamine and the oligonucleotide is about 3:1.

Fig. 1a shows a scanning electron micrograph of a synthetic particle with negative surface charge. The ratio by weight between protamine and oligonucleotide in this case was 1:2. Fig. 1b shows a synthetic particle with positive surface charge. The ratio by weight between protamine and oligonucleotide in this case was 2.5:1.

Fig. 2 shows the dependence of the incubation time on the protamine/oligonucleotide ratio by weight. The particle size increases with increasing incubation time. It is thus possible to adjust any desired particle sizes.

Fig. 3 shows the dependence of the zeta potential on the protamine/oligonucleotide ratio by weight. As the protamine content increases, the zeta potential is shifted to positive values.

Figs. 4a and b show comparatively the uptake of oligonucleotides by means of synthetic particles (Fig. 4a) in vero cells. Fig. 4b shows a control incubation of dissolved oligonucleotides. The oligonucleotide concentration is 5 µg/ml with an incubation time of four hours at 37°C and 5% CO_2. It is evident that the uptake of oligonucleotides in cells is increased on use of the synthetic particles according to the invention.

Fig. 5 shows the stability of the particles according to the invention to enzymatic degradation by endonucleases. The UV absorption at 260 nm is plotted against the retention time for various

protamine/oligonucleotide ratios. The results show that the particle according to the invention ensures virtually quantitative protection from enzymatic degradation.

Patent Claims

1. Synthetic particle formed from at least one nucleic acid sequence or nucleic acid derivative sequence and one protein having a molecular weight in the range from 3900 to 4300.

2. Synthetic particle according to Claim 1, where the protein consists predominantly of arginine.

3. Synthetic particle according to Claim 1 or 2, where the protein is selected from the following group: protamine, protamine base, protamine derivatives or salts, preferably protamine sulfate or protamine chloride.

4. Synthetic particle according to any of the preceding claims, where the nucleic acid sequence is in single-stranded form.

5. Synthetic particle according to any of the preceding claims, where the nucleic acid sequence is an oligonucleotide or a derivative thereof.

6. Synthetic particle according to any of the preceding claims, where the oligonucleotide consists of at least 5 nucleotides.

7. Synthetic particle according to any of the preceding claims, where the derivative is a phosphorothioate or an anionic derivative.

8. Synthetic particle according to any of the preceding claims, where the average diameter of the particle is in the range from 10 nm to 100 µm.

9. Synthetic particle according to any of the preceding claims, where the particle carries a surface electric charge.

10. Synthetic particle according to any of the preceding claims, where the surface charge is in the range from -40 mV to +40 mV.

11. Process for the preparation of synthetic particles according to any of the preceding claims, with the following steps:

a) preparation of an aqueous first solution containing a protein having a molecular weight in the range from 3900 to 4300,

b) addition to the first solution of a second solution containing a nucleic acid sequence or nucleic acid derivative sequence and

c) mixing of the first and second solution.

12. Process according to Claim 11, where the first and the second solution are free of salts.

13. Process according to either of Claims 11 or 12, where the molar ratio of nucleic acid sequence or nucleic acid derivative sequence to protein is adjusted to produce a predetermined surface charge.

14. Process according to any of Claims 11 to 13, where the protein consists predominantly of arginine.

15. Process according to any of Claims 11 to 14, where the protein is selected from the following group: protamine, protamine base, protamine derivatives

or salts, preferably protamine sulfate or protamine chloride.

16. Process according to Claim 15, where protamine, protamine base, protamine derivatives are obtained from salmon sperm.

17. Process according to any of Claims 11 to 16, where the nucleic acid sequence is in single-stranded form.

18. Process according to Claim 17, where the nucleic acid sequence is an oligonucleotide or a derivative thereof.

19. Process according to Claim 18, where the oligonucleotide consists of at least 5 nucleotides.

20. Process according to any of Claims 17 to 19, where the derivative is a phosphorothioate or an anionic derivative.

21. Process according to any of Claims 11 to 20, where the diameter of the particle is in the range from 10 nm to 100 µm.

22. Process according to any of Claims 11 to 21, where the particle carries a surface electric charge.

23. Process according to any of Claims 9 to 22, where the surface charge is in the range from -40 mV to +40 mV.

24. Use of a protein having a molecular weight in the range from 3900 to 4300 for the preparation of a synthetic particle containing at least one nucleic acid sequence or nucleic acid derivative sequence.

25. Use according to Claim 24, where the protein consists predominantly of arginine.

26. Use according to Claim 24 or 25, where the protein is selected from the following group: protamine, protamine base, protamine derivatives or salts, preferably protamine sulfate or protamine chloride.

27. Use according to any of Claims 24 to 26, where the nucleic acid is an oligonucleotide which is preferably single stranded and preferably consists of at least 5 nucleotides, or a derivative thereof which is preferably in the form of a phosphorothioate.

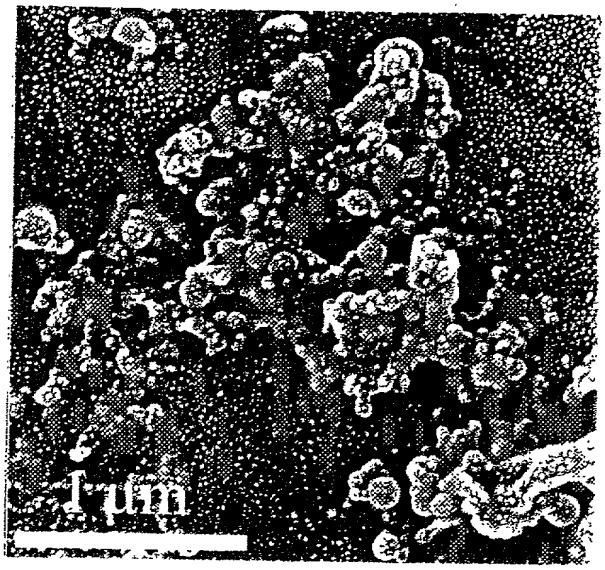


Fig. 1a

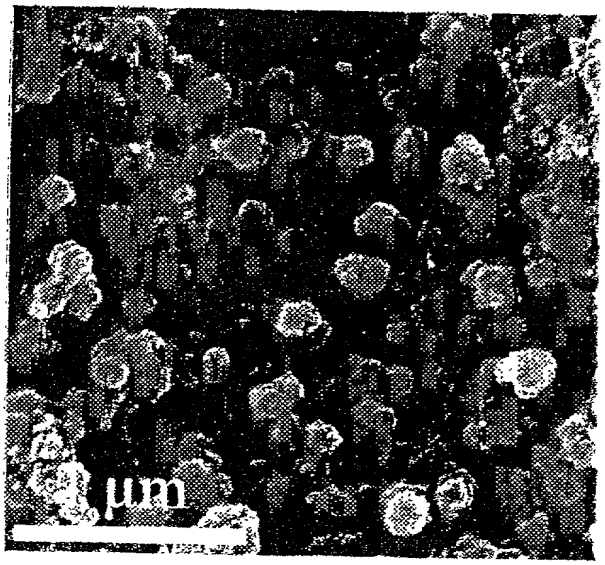
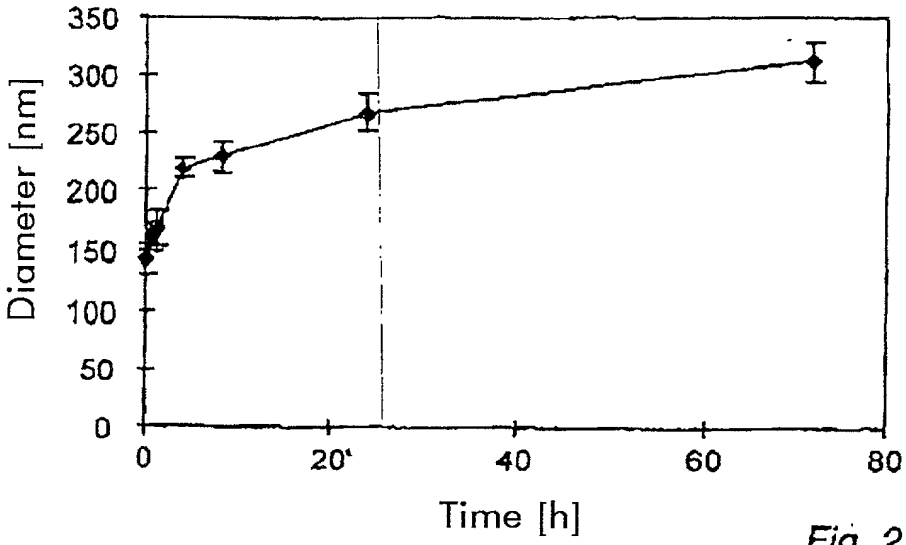


Fig. 1b


Diameter [nm]
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300
250
200
150
100
50
0
0
20'
40
60
80
Time [h]

Fig. 2

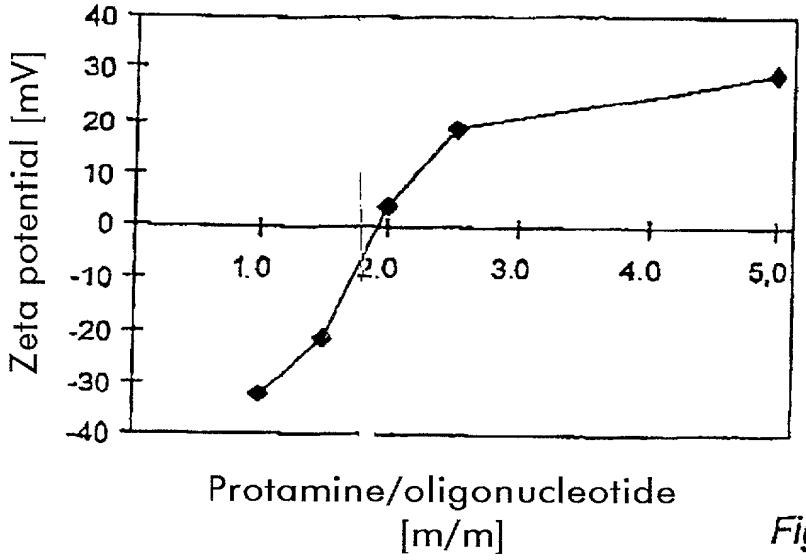
Zeta potential [mV]
40
30
20
10
0
-10
-20
-30
-40
1.0
2.0
3.0
4.0
5,0
Protamine/oligonucleotide
[m/m]

Fig. 3

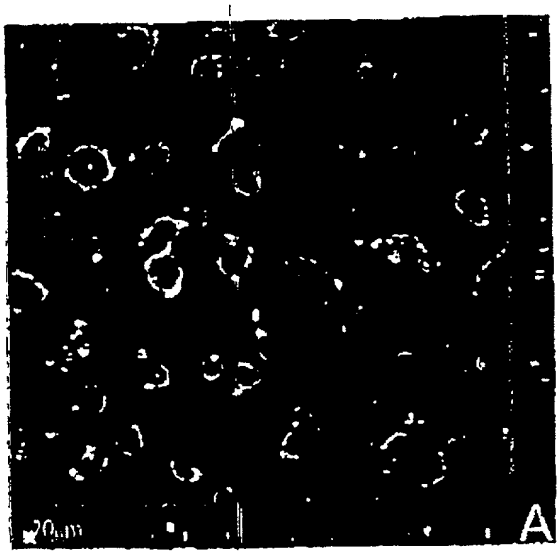

Fig. 4a

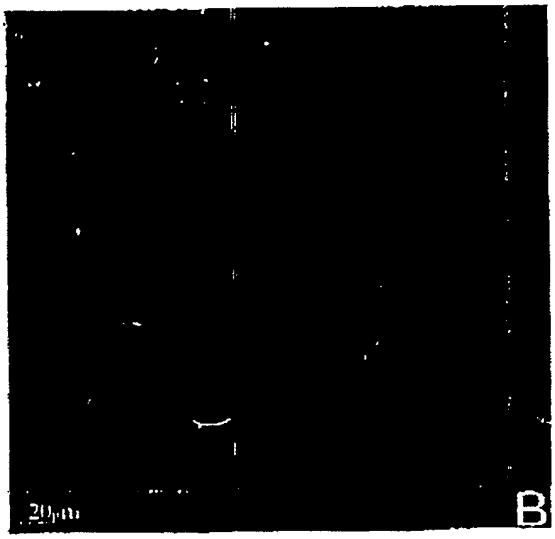

Fig. 4b

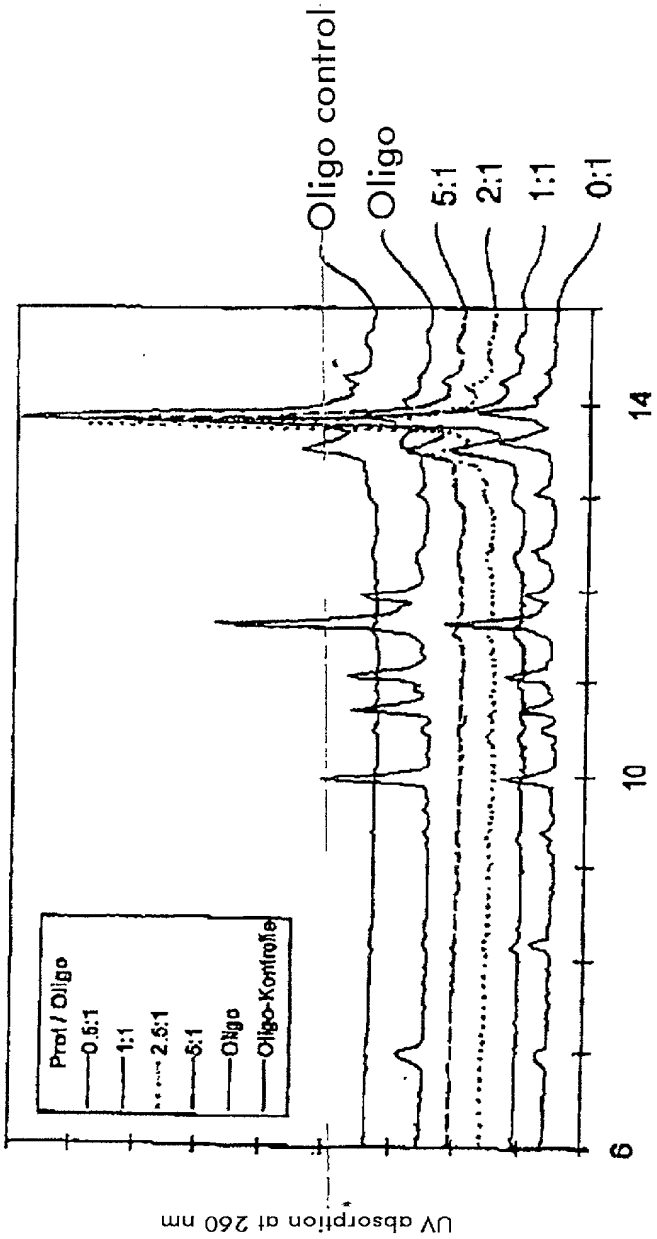
Oligo control
Oligo
5:1
2:1
1:1
0:1
Prot / Oligo
0.5:1
1:1
2.5:1
5:1
Oligo
Oligo-Kontrolle
6
10
14
Retention time [min]
UV absorption at 260 nm

Fig. 5

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Monika Junghans et al.

Serial No.: 09/868,215

Filed: June 14, 2001

Title: SYNTHETIC NUCLEIC ACID PARTICLE

Docket No.: WFG-12544

LETTER

Attn: Ms. Anita Johnson
Fax No.: 703-305-3230
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

We have received a "Notification of Missing Requirements" (copy attached) dated August 10, 2001 in the above-identified application advising that the declaration of the inventors is missing in this application. The required Declaration and Power of Attorney for the above-identified application was sent on June 26, 2001. The $65.00 late filing fee surcharge for a small entity was included in the filing fee sent on June 14, 2001. Attached hereto is a copy of the declaration that was originally sent on June 26, 2001, along with a copy of the return receipt postcard indicating receipt by the Patent Office on June 28, 2001.

Accordingly, all the missing parts of the application have been filed and no further action is required. If there are any further fees resulting from this communication not covered by the enclosed check, or if no check was enclosed, please charge the same to Deposit Account No. 18-0160, Order No. WFG-12544.

Respectfully submitted,

RANKIN, HILL, PORTER & CLARK LLP

By _____
David E. Spaw, Reg. No. 34732

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Customer No. 007609

I hereby certify that this correspondence is being facsimile transmitted to the Patent and Trademark Office (Fax No. (703) 305-3230) on the date indicated below.

_____
Signature

8/20/01 David E. Spaw
Date Printed Name of Person Signing this Certificate

november 78/US

PTO/SB/81A (10-00)
Approved for use through 10/31/2002. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

As the below named inventor(s), I/we declare that:

This declaration is directed to:

☐ The attached application, or

☒ Application No. PCT/DE99/03974, filed on December 13, 1999,

☒ as amended on 21.02.2001 (if applicable);

I/we believe that I/we am/are the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought;

I/we have reviewed and understand the contents of the above-identified application, including the claims, as amended by any amendment specifically referred to above;

I/we acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me/us to be material to patentability as defined in 37 CFR 1.56, including material information which became available between the filing date of the prior application and the National or PCT International filing date of the continuation-in-part application, if applicable; and

All statements made herein of my/own knowledge are true, all statements made herein on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and may jeopardize the validity of the application or any patent issuing thereon.

FULL NAME OF INVENTOR(S)

100 Inventor one: Monika Junghans Date: 13. Juni 2001
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300 Inventor three: Jörg Kreuter Date: 8. Jun. 2001
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Signature: Citizen of:

☐ Additional inventors are being named on additional form(s) attached hereto.

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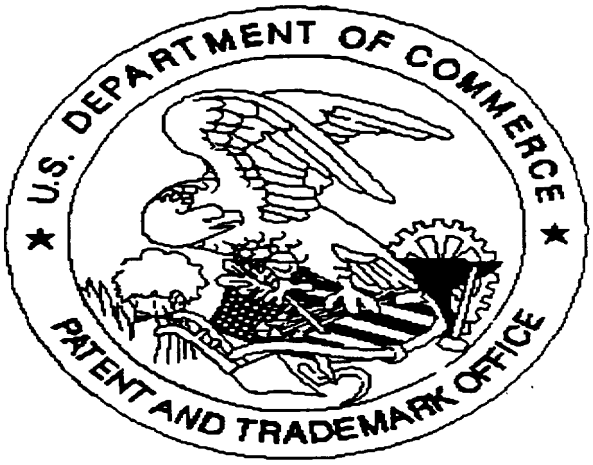

Application deficiencies found during scanning:

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☛ ***Scanned copy is best available.*** Drawings figures 1ª, 1ᵇ, 4ª, 4ᵇ are very dark